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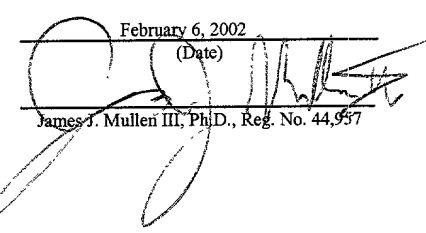
Applicant : K. Gehlsen

) Group Art Unit Unknown

Appl. No. : Unknown

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) Arlington, VA 22202, on

Filed : Herewith

For : METHODS AND
COMPOSITIONS FOR
TOPICAL TREATMENT OF
DAMAGED TISSUE USING
REACTIVE OXYGEN
METABOLITE PRODUCTION
OR RELEASE INHIBITORS) February 6, 2002
) (Date)
) 
) James J. Mullen III, Ph.D., Reg. No. 44,957

Examiner : Unknown

PRELIMINARY AMENDMENT

United States Patent and Trademark Office
PO Box 2327
Arlington, VA 22202

Dear Sir:

Prior to examination and prior to the calculation of fees, please amend the above-referenced patent application as follows:

IN THE SPECIFICATION

Please replace **Paragraph [0009]** with the following rewritten paragraph:

[0009] The enzyme activity is almost undetectable in resting (unstimulated) phagocytes, but increases dramatically upon stimulation. Patients with the rare genetic disorder chronic granulomatous disease (CGD), have a severe predisposition to chronic recurrent infection. The neutrophils from these patients phagocytose normally but the respiratory burst is absent and NADPH oxidase activity (and radical production) is undetectable,

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indicating that the oxidase and its product, the reactive oxygen metabolites (ROMs), have an important bactericidal function.

Please replace **Paragraph [0012]** with the following rewritten paragraph:

[0012] Topically administered salves, balms and other such medicaments are well known in the art. The application of mud or plant extracts such as aloe vera are just two examples of such medicaments. For a discussion of aloe vera, see U.S. Patent No. 4,857,328, which is hereby incorporated by reference. The use of two different histamine derivatives as topically administered skin medicaments has also been discussed previously. The first may be found in a series of U.S. Patents to Jack et al., which disclose the use of a pharmaceutical composition of water, water soluble vinyl polymer gel, an amine alcohol dispersant and 1H-imidazole-4-ethanamine phosphate to treat certain skin disorders. See U.S. Patent Nos. 5,294,440; 5,679,337; and 5,716,610. The second is found in U.S. Patent No. 5,792,784, which discloses a pseudo-dipeptide product obtained by coupling histamine or a methyl-substituted histamine and an amino acid.

Please replace **Paragraph [0019]** with the following rewritten paragraph:

[0019] The compositions of the present invention can be found in a variety of cosmetic illusions. For example, the composition can be a lipstick, a shampoo, a carrier, a mouthwash, or a transdermal patch.

Please replace **Paragraph [0020]** with the following rewritten paragraph:

[0020] The present invention relates to compositions and methods for the reduction of reactive oxygen mediated damage in the treatment of skin and mucosal membrane disorders caused by or aggravated by reactive oxygen metabolites (ROMs). The compositions and methods of the present invention are useful, for example, for treating certain disorders caused by various disease etiologies, and lesions of the skins, such as burns.

Please replace **Paragraph [0030]** with the following rewritten paragraph:

[0030] The present invention contemplates using various histamine or histamine-related compounds to achieve a beneficial reduction in the concentration of enzymatically produced ROM production and release. The

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present invention is also directed to inhibition of ROM production and release. The term "histamine" as used herein incorporates a variety of histamine and histamine related compounds. For example, histamine, the dihydrochloride salt form of histamine (histamine dihydrochloride), histamine diphosphate, other histamine salts, esters, or prodrugs, and H₂ receptor agonists are to be included. The topical administration of compounds that induce the release of endogenous histamine from a patient's own tissue stores is also included within the scope of the present invention. Such compounds include IL-3 retinoic acid, other retinoids such as 9-cis-retinoic acid and all-trans-retinoic acid, and allergens. Other ROM production and release inhibitory compounds such as NADPH oxidase inhibitors like diphenyleneiodonium are also within the scope of the present invention. The topical administration of serotonin and 5HT agonists in the present invention is also contemplated.

Please replace **Paragraph [0048]** with the following rewritten paragraph:

[0048] Suitable moisturizers for use in the formulations of the present invention include, but are not limited to lactic acid and other hydroxy acids and their salts, glycerin, propylene glycol, and butylene glycol. Suitable emollients include lanolin alcohol, lanolin, lanolin derivatives, cholesterol, petrolatum, isostearyl neopentanoate and mineral oils. In addition, combinations or mixtures of these moisturizers and emollients can be used in the formulations of the present invention.

Please replace **Paragraph [0066]** with the following rewritten paragraph:

[0066] Steady state reservoirs for use with the compounds of the present invention will delivery a suitable dose of those compounds over a predetermined period of time. Compositions and methods of manufacturing compositions capable of absorption through the mucosal tissues are taught in U.S. Patent No. 5,288,497, which is hereby incorporated by reference. One of skill in the art would readily know how to include the compounds of the present invention in these and related compositions.

Please replace **Paragraph [0083]** with the following rewritten paragraph:

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[0083] A female subject suffering from herpes genitalis is treated with the ROM inhibitory compound histamine diphosphate in a concentration of 0.07% by weight of formulation in the form of a foam and a cream. Using an applicator, the foam is injected into the vaginal space to treat herpetic lesions therein. The cream is applied topically to external lesions. The cream and foam are applied three times a day for a period of five days. There are no untoward reactions and the treatment reduces the healing time of the ruptured herpetic vesicles.

Please replace **Paragraph [0085]** with the following rewritten paragraph:

[0085] A subject suffering from pharyngotonsillitis, a herpetic infection of the pharyngeal region is treated with a mouthwash containing the ROM inhibitory compound NADPH oxidase inhibitor diphenyleneiodonium in a concentration of 0.05% by weight of formulation. The treatment consists of five mouthwash applications per day for a period of seven days. The administration of diphenyleneiodonium is effective in treating the pharyngotonsillitis of the subject.

Please replace **Paragraph [0105]** with the following rewritten paragraph:

[0105] The compositions of the present invention are administered topically to a subject presenting thermal burn injuries. A water-based gel preparation containing of 0.007% by weight of the formulation of serotonin is administered to the subject's burn injuries. The treatment consists of topical application of the gel to the burn site every 10 minutes for the first hour, then every 30 minutes for the next three hours. Topical applications thereafter are applied as needed by the subject in response to pain. Application of the gel reduces the discomfort of the subject and promotes healing of the burn injuries.

Please replace **Paragraph [0106]** with the following rewritten paragraph:

[0106] The compositions of the present invention are administered topically to a subject presenting chemical burn injuries. A water-based gel preparation containing of 0.007% by weight of the formulation of histamine dihydrochloride is administered to the subject's burn injuries. The treatment

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consists of topical application of the gel to the burn site every 10 minutes for the first hour, then every 30 minutes for the next three hours. Topical applications thereafter are applied as needed by the subject in response to pain. Application of the gel reduces the discomfort of the subject and promotes healing of the burn injuries.

Please replace **Paragraph [0110]** with the following rewritten paragraph:

[0110] A subject having undergone the procedure of a chemical peel is treated with a solution containing 0.008% by weight of histamine dihydrochloride to ease the tissue damage caused by the procedure and to promote healing of the treated skin. The solution is applied by soaking the treated area five times daily. The rate of healing is increased in those area treated with the solution.

Please replace **Paragraph [0117]** with the following rewritten paragraph:

[0117] Because gum disease is usually painless, however, it often goes undetected. In the more advanced stages of gum disease, called periodontitis, the gums and bone that support the teeth can become seriously damaged. The teeth can become loose, fall out or have to be removed by a dentist. Symptoms of periodontal disease include: gums that bleed when the teeth are brushed; red, swollen or tender gums; gums that have pulled away from the teeth; bad breath that doesn't go away; pus between the teeth and gums; loose teeth; a change in the way the teeth fit together when biting; or a change in the fit of partial dentures.

IN THE CLAIMS

Kindly cancel claims 1-25.

Please add the following claims:

26. (New) A method for making a cosmetic composition for topically delivering a compound that inhibits the production and release of enzymatically produced ROMs comprising:

providing a cosmetically acceptable carrier and a compound selected from the group consisting of histamine, histamine dihydrochloride, histamine diphosphate, other histamine salts, esters, prodrugs, histamine-receptor agonists, serotonin, and 5HT

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agonists in a concentration effective to treat ROM mediated damage to the skin caused by a disorder of the skin selected from the group consisting of herpes labialis, herpes genitalis, herpes zoster, varicella zoster, bacterial infections, chemotherapy-induced mucositis, radiotherapy-induced mucositis, photodermatitis, thermal burns, cosmetic surgery and periodontal disease; and

forming a composition containing the cosmetically carrier and said compound that inhibits the production and release of enzymatically produced ROMs.

27. (New) The method of Claim 26, wherein said compound is a compound that promotes the release of endogenous histamine stores.
28. (New) The method of Claim 27, wherein said endogenous histamine releasing compound is selected from a group consisting of IL-3, retinoic acid, 9-cis-retinoic acid, all-trans-retinoic acid, and allergens.
29. (New) The method of Claim 26, wherein said composition is a lipstick.
30. (New) The method of Claim 26, wherein said composition is a shampoo.
31. (New) The method of Claim 26, wherein said cosmetically acceptable carrier is a spray.
32. (New) The method of Claim 26, wherein said cosmetically acceptable carrier is a mouthwash.
33. (New) The method of Claim 26, wherein said cosmetically acceptable carrier is a transdermal patch.
34. (New) A cosmetic composition comprising an effective dose of a compound that inhibits the enzymatic production or release of ROMs in a cosmetically acceptable carrier adapted for topical delivery, wherein said carrier is selected from the group consisting of a sunscreen, a toothpaste, a soap, a wound dressing, a spray, a mouthwash, and a transdermal patch.
35. (New) The composition of Claim 34, wherein said compound is selected from the group consisting of histamine, histamine dihydrochloride, histamine diphosphate, other histamine salts, esters, prodrugs, H₂ receptor agonists, serotonin, and 5HT agonists.
36. (New) The composition of Claim 34, wherein said compound is a compound that promotes the release of endogenous histamine stores.
37. (New) The composition of Claim 36, wherein said compound that promotes the release of endogenous histamine stores is selected from the group consisting of IL-3, retinoic acid, 9-cis-retinoic acid, all-trans-retinoic acid, and allergens.

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38. (New) The composition of Claim 34, wherein the cosmetically acceptable carrier further comprises a colorant.

39. (New) The composition of Claim 38, wherein the colorant is selected from the group consisting of FD&C Red No. 40 and FD&C Yellow No. 5.

40. (New) The composition of Claim 34, wherein the cosmetically acceptable carrier further comprises a fragrance.

41. (New) The composition of Claim 34, wherein the cosmetically acceptable carrier further comprises a moisturizer.

REMARKS

Applicant respectfully requests the examiner to consider the above-captioned application in view of the foregoing amendments and the following comments. The specification has been amended to correct minor typographical errors. Claims 1-25 have been cancelled. Claims 26-41 have been added.

Support for the amendments can be found throughout the original specification and claims. Support for claims 26-28 can be found, for example, at paragraphs [0030] through [0032]. Support for claims 27, 28, 36 and 37 can be found, for example, at paragraph [0030]. Claims 29-32 find support in the specification at, for example, paragraphs [0041] and [0052]. Claim 33 is supported by the specification at, for example, paragraphs [0061]-[0063]. Claims 34 and 35 find support at, for example, paragraphs [0030], [0041], [0042], [0054], and [0055]. Claims 38-41 are supported at, for example, paragraphs [0048], [0050], and [0052]. Accordingly, no new matter has been added by these amendments. Claims 26-41 are presented for examination.

The specific changes to the specification are shown on a separate set of pages attached hereto and entitled VERSION WITH MARKINGS TO SHOW CHANGES MADE, which follows the signature page of this Preliminary Amendment. On this set of pages the insertions are underlined while deleted text is [bracketed].

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

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Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 6 Feb 2002

By: 

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Registration No. 44,957

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**VERSION WITH MARKINGS TO SHOW CHANGES MADE TO THE
SPECIFICATION**

Paragraph [0009] has been amended as follows:

[0009] The enzyme activity is almost undetectable in resting (unstimulated) phagocytes, but increases dramatically upon stimulation. Patients with the rare genetic disorder chronic granulomatous disease (CGD), have a severe predisposition to chronic recurrent infection. The neutrophils from these patients phagocytose normally but the respiratory burst is absent and NADPH oxidase activity (and radical production) is undetectable, indicating that the oxidase and its product, the reactive oxygen metabolites (ROMs), have an important bactericidal function.

Paragraph [0012] has been amended as follows:

[0012] Topically administered salves, balms and other such medicaments are well known in the art. The application of mud or plant extracts such as aloe vera are just two examples of such medicaments. For a discussion of aloe vera, see U.S. Patent No. 4,857,328, which is hereby incorporated by reference. The use of two different histamine derivatives as topically administered skin medicaments has also been discussed previously. The first may be found in a series of U.S. Patents to Jack et al., which disclose the use of a pharmaceutical composition of water, water soluble vinyl polymer gel, an amine alcohol dispersant and 1H-imidazole-4-ethanamine phosphate to treat certain skin disorders. See U.S. Patent Nos. 5,294,440; 5,679,337; and 5,716,610. The second is found in U.S. Patent No. 5,792,784, [that] which discloses a pseudo-dipeptide product obtained by coupling histamine or a methyl-substituted histamine and an amino acid.

Paragraph [0019] has been amended as follows:

[0019] The compositions of the present invention can be found in a variety of cosmetic [illusion] illusions. For example, the composition can be a lipstick, a shampoo, a carrier, a mouthwash, or a transdermal patch.

Paragraph [0020] has been amended as follows:

[0020] The present invention relates to compositions and methods for the reduction of reactive oxygen metabolite mediated damage in the treatment of skin and mucosal membrane

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disorders caused by or aggravated by reactive oxygen metabolites (ROMs). The compositions and methods of the present invention are useful, for example, for treating certain disorders caused by various disease etiologies, and lesions of the skin, such as burns.

Paragraph [0030] has been as follows:

[0030] The present invention contemplates using various histamine or histamine-related compounds to achieve a beneficial reduction in the concentration of enzymatically produced ROM production and release. The present invention is also directed **[at]** to inhibition of ROM production and release. The term "histamine" as used herein incorporates a variety of histamine and histamine related compounds. For example, histamine, the dihydrochloride salt form of histamine (histamine dihydrochloride), histamine diphosphate, other histamine salts, esters, or prodrugs, and H₂ receptor agonists are to be included. The topical administration of compounds that induce the release of endogenous histamine from a patient's own tissue stores is also included within the scope of the present invention. Such compounds include IL-3 retinoic acid, other retinoids such as 9-cis-retinoic acid and all-trans-retinoic acid, and allergens. Other ROM production and release inhibitory compounds such as NADPH oxidase inhibitors like **[diphenyleneiodonium]** diphenyleneiodonium are also within the scope of the present invention. The topical administration of serotonin and 5HT agonists in the present invention is also contemplated.

Paragraph [0048] has been amended as follows:

[0048] Suitable moisturizers for use in the formulations of the present invention include, but are not limited to lactic acid and other hydroxy acids and their salts, glycerin, **[propylene]** propylene glycol, and butylene glycol. Suitable emollients include lanolin alcohol, lanolin, lanolin derivatives, cholesterol, petrolatum, isostearyl neopentanoate and mineral oils. In addition, combinations or mixtures of these moisturizers and emollients can be used in the formulations of the present invention.

Paragraph [0066] has been amended as follows:

[0066] Steady state reservoirs for use with the compounds of the present invention will delivery a suitable dose of those compounds over a predetermined period of time. Compositions and methods of manufacturing compositions capable of absorption through the

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mucosal tissues are taught in U.S. Patent No. 5,288,497, which is hereby incorporated by reference. One of skill in the art **[could]** would readily know how to include the compounds of the present invention in these and related compositions.

Paragraph [0083] has been amended as follows:

[0083] A female subject suffering from herpes genitalis is treated with the ROM inhibitory compound histamine diphosphate in a concentration of 0.07% by weight of formulation in the form of a foam and a cream. Using an applicator, the foam is injected into the vaginal space to treat herpetic lesions therein. The cream is applied topically to external lesions. The cream and foam are applied three times a day for a period of five days. There are no untoward reactions and the treatment **[reduced]** reduces the healing time of the ruptured herpetic vesicles.

Paragraph [0085] has been amended as follows:

[0085] A subject suffering from **[pharyngotosillitis]** pharyngotonsillitis, a herpetic infection of the pharyngeal region is treated with a mouthwash containing the ROM inhibitory compound NADPH oxidase inhibitor **[diphenyleneiodonium]** diphenyleneiodonium in a concentration of 0.05% by weight of formulation. The treatment consists of five mouthwash applications per day for a period of seven days. The administration of **[diphenyleneiodonium]** diphenyleneiodonium **[was]** is effective in treating the **[pharyngotosillitis]** pharyngotonsillitis of the subject.

Paragraph [0105] has been amended as follows:

[0105] The compositions of the present invention are administered topically to a subject presenting thermal burn injuries. A water-based gel preparation containing of 0.007% by weight of the formulation of serotonin **[was]** is administered to the subject's burn injuries. The treatment **[consisted]** consists of topical application of the gel to the burn site every 10 minutes for the first hour, then every 30 minutes for the next three hours. Topical applications thereafter are applied as needed by the subject in response to pain. Application of the gel reduces the discomfort of the subject and promotes healing of the burn injuries.

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Paragraph [0106] has been amended as follows:

[0106] The compositions of the present invention are administered topically to a subject presenting chemical burn injuries. A water-based gel preparation containing of 0.007% by weight of the formulation of histamine dihydrochloride [~~was~~] is administered to the subject's burn injuries. The treatment [~~consisted~~] consists of topical application of the gel to the burn site every 10 minutes for the first hour, then every 30 minutes for the next three hours. Topical applications thereafter are applied as needed by the subject in response to pain. Application of the gel reduces the discomfort of the subject and promotes healing of the burn injuries.

Paragraph [0110] has been amended as follows:

[0110] A subject having undergone the procedure of a chemical peel is treated with a solution containing 0.008% by weight of histamine dihydrochloride to ease the tissue damage caused by the procedure and to promote healing of the treated skin. The solution is applied by soaking the treated area five times daily [~~to the treated area~~]. The rate of healing is increased in those area treated with the solution.

Paragraph [0117] has been amended as follows:

[0117] Because gum disease is usually painless, however, it often goes undetected. In the more advanced stages of gum disease, called periodontitis, the gums and bone that support the teeth can become seriously damaged. The teeth can become loose, fall out or have to be removed by a dentist. Symptoms of periodontal disease include: gums that bleed when the teeth are brushed; red, swollen or tender gums; gums that have pulled away from the teeth; bad breath that doesn't go away; pus between the teeth and gums; loose teeth; a change in the way the teeth fit together when biting; or a change in the fit of partial dentures.

IN THE CLAIMS

Kindly cancel claims 1 - 25.

Please add claims 26 - 41.